BOOKS

1) Organic Chemistry Structure and Function, K. Peter C. Vollhardt, Neil Schore, 6th Edition

2) Organic Chemistry, T. W. Graham Solomons, Craig B. Fryhle

3) Organic Chemistry: A Short Course, H. Hart, L. E. Craine, D. J. Hart, C. M. Hadad,

4) Organic Chemistry: A Brief Course, R. C. Atkins, F.A. Carey

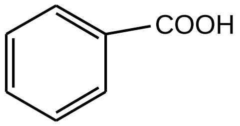
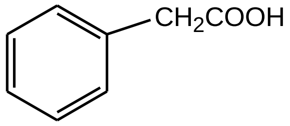
4. CARBOXYLIC ACIDS AND THEIR DERIVATIVES

4. CARBOXYLIC ACIDS AND THEIR DERIVATIVES

The carboxyl group, (abbreviated CO_2H or COOH), is one of the most widely occurring functional groups in chemistry and biochemistry. Not only are carboxylic acids themselves important, but the carboxyl group is the parent group of a large family of related compounds called acyl compounds or carboxylic acid derivatives.

4.1 Nomenclature of Carboxylic Acids

Systematic or substitutive names for carboxylic acids are obtained by dropping the final -e of the name of the alkane corresponding to the longest chain in the acid and by adding -oic acid. The carboxyl carbon atom is assigned number 1. Many carboxylic acids have common names that are derived from Latin or Greek words that indicate one of their natural sources.

Structure	IUPAC Name	Common Name
HCOOH	Methanoic acid	Formic acid
CH_3COOH	Ethanoic acid	Acetic acid
$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid
$CH_3CH(OH)COOH$	2-Hydroxypropanoic acid	Lactic acid
$CH_2{=}CHCOOH$	Propenoic acid	Acrylic acid
	Benzenecarboxylic acid	Benzoic acid
	2-Phenylethanoic acid	Phenylacetic acid

4.2 Carboxylate Salts

Salts of carboxylic acids are named as -ates; in both common and systematic names, -ate replaces -ic acid. The name of the cation precedes that of the carboxylate anion. Sodium and potassium salts of most carboxylic acids are readily soluble in water. This is true even of the long-chain carboxylic acids. Water-insoluble carboxylic acids dissolve in either aqueous sodium hydroxide or aqueous sodium bicarbonate.

$$CH_3COOH + NaOH \longrightarrow CH_3COONa + H_2O$$

$$2CH_3COOH + Na_2CO_3 \longrightarrow 2CH_3COONa + H_2O + CO_2$$

$$CH_3COOH + NaCH2O_3 \longrightarrow CH_3COONa + H_2O + CO_2$$

4.3 Synthesis of Carboxylic Acids

1. By oxidation of aldehydes and primary alcohols

Aldehydes can be oxidized to carboxylic acids with mild oxidizing agents such as $Ag(NH_3)_2^+OH^-$. Primary alcohols can be oxidized with $KMnO_4$. Aldehydes and primary alcohols are oxidized to carboxylic acids with chromic acid (H_2CrO_4) in aqueous acetone.

$$RCH_2OH \xrightarrow{[O]} RCOH \xrightarrow{[O]} RCOOH$$

$$CH_3CH_2COH \xrightarrow{KMnO_4/\ H_2O} CH_3CH_2COOH + NO_2 + H_2O$$

$$CH_3CH{=}CHCH_3 \xrightarrow{H_2O_2} 2CH_3COOH$$

2. By hydrolysis of cyanohydrins and other nitriles

In the hydrolysis the CN group is converted to a CO_2H group. Nitriles can also be prepared by nucleophilic substitution reactions of alkyl halides with sodium cyanide. Hydrolysis of the nitrile yields a carboxylic acid with a chain one carbon atom longer than the original alkyl halide.

$$RX + NaCN \xrightarrow[-\ NaX]{} RCN \xrightarrow[-NH_4^{\oplus}]{H^{\oplus}/\ H_2O} RCOOH$$

$$CH_3CH_2CHO \xrightarrow[2)HCl/H_2O]{1)NaCN/H_2O} CH_3CH_2CH(OH)COOH$$

3. By oxidation of alkylbenzenes

Primary and secondary alkyl groups (but not 3° groups) directly attached to a benzene ring are oxidized by $KMnO_4$ to a CO_2H group.

4. By carbonation of Grignard reagents.

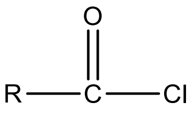
Grignard reagents react with carbon dioxide to yield magnesium carboxylates. Acidification produces carboxylic acids.

$$RMgX + CO_2 \longrightarrow RCOOMgX \xrightarrow{HCl/\ H_2O} RCOOH$$

$$CH_3CH_2CH_2CH_2MgCl + CO_2 \xrightarrow{HCl/\ H_2O} CH_3CH_2CH_2CH_2COOH$$

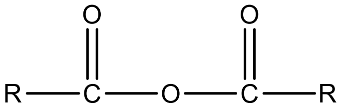
4.4 Carboxylic Acids Derivatives

RCOX (X: OR, OCOR, NH_2, Halogen)



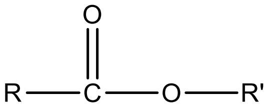
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl$$

Acyl Chlorides



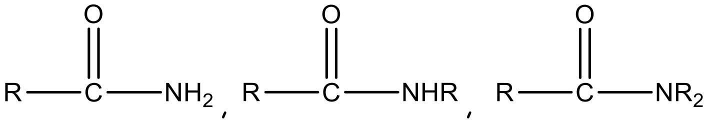
$R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R$

Acid Anhydrides



$R-\overset{O}{\overset{\|}{C}}-O-R'$

Esters

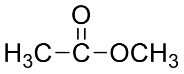


$R-\overset{O}{\overset{\|}{C}}-NH_2$, $R-\overset{O}{\overset{\|}{C}}-NHR$, $R-\overset{O}{\overset{\|}{C}}-NR_2$

Amides

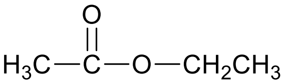
4.5 Esters

Carboxylic acids react with alcohols to form esters through a condensation reaction known as esterification



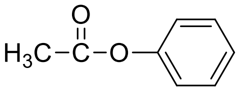
$H_3C-\overset{O}{\overset{\|}{C}}-OCH_3$

Methyl acetate



$H_3C-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3$

Ethyl acetate

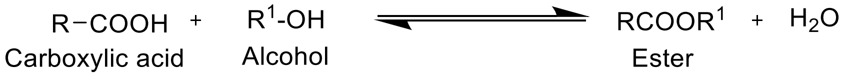


Phenyl acetate

4.6 Synthesis of Esters

Fischer Esterifications

Acid-catalyzed esterifications, such as these examples, are called Fischer esterifications. Fischer esterifications proceed very slowly in the absence of strong acids, but they reach equilibrium within a matter of a few hours when an acid and an alcohol are refluxed with a small amount of concentrated sulfuric acid or hydrogen chloride.



$$R-COOH + R^1\text{-}OH \rightleftharpoons RCOOR^1 + H_2O$$

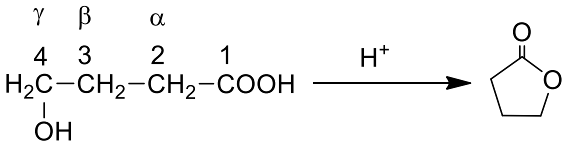
Schotten Baumann Reaction

The reaction of acyl chlorides with alcohols is one of the best ways to synthesize an ester. The reaction of an acyl chloride with an alcohol to form an ester occurs rapidly and does not require an acid catalyst. Pyridine is often added to the reaction mixture to react with the HCl that forms.

$$\underset{\text{Alcohol}}{\text{R-OH}} + \underset{\text{Acyl chloride}}{\text{R}^1\text{-COCl}} \xrightarrow{\text{Pyridine, } 20^{o}\text{C}} \underset{\text{Ester}}{\text{R}^1\text{-COOR}}$$

Lactons

Carboxylic acids whose molecules have a hydroxyl group on a γ- or δ-carbon undergo an intramolecular esterification to give cyclic esters known as γ- or δ- lactones. The reaction is acid catalyzed:



γ-Valerolactone

4.7 Base-Promoted Hydrolysis of Esters: Saponification

Esters undergo base-promoted hydrolysis as well as acid hydrolysis. Base-promoted hydrolysis is called saponification.

$$\text{RCOOR}^1 + \text{NaOH} \longrightarrow \underset{\text{soap}}{\text{RCOONa}} + \text{R}^1\text{OH}$$

4.8 Ammonolysis of Esters

Esters undergo nucleophilic addition–elimination at their acyl carbon atoms when they are treated with ammonia (called ammonolysis) or with primary and secondary amines. See section 4.16

4.9 Grignard Reaction with Esters

When a Grignard reagent adds to the carbonyl group of an ester, the initial product is unstable and loses a magnesium alkoxide to form a ketone. Ketones, however, are more reactive toward Grignard reagents than esters. Therefore, as soon as a molecule of the ketone is formed in the mixture, it reacts with a second molecule of the Grignard reagent. After hydrolysis, the product is a tertiary alcohol.

4.10 Reduction of Esters

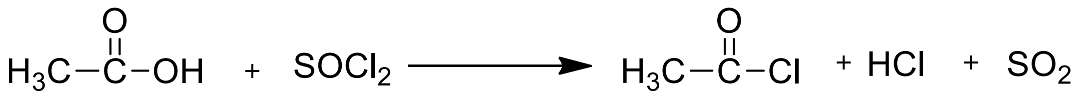
Lithium aluminum hydride ($LiAlH_4$, abbreviated LAH) reduces carboxylic acids and esters to primary alcohols. LAH reduction of an ester yields two alcohols, one derived from the carbonyl part of the ester group, and the other from the alkoxyl part of the ester.

$$RCOOR^1 + LiAlH_4 \longrightarrow RCH_2OH + R^1OH$$

4.14 Acyl Halides

Acyl chlorides are also called acid chlorides. They are named by dropping -ic acid from the name of the acid and then adding -yl chloride.

Since acyl chlorides are the most reactive of the acid derivatives, we must use special reagents to prepare them. We use PCl_5 (an acid chloride of phosphoric acid), PCl_3 (an acid chloride of phosphorous acid), and $SOCl_2$ (an acid chloride of sulfurous acid).



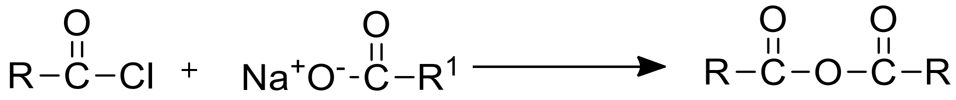
$$H_3C-\overset{O}{\overset{\|}{C}}-OH + SOCl_2 \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-Cl + HCl + SO_2$$

Acetic acid Thyonyl chloride Acetyl chloride

4.12 Carboxylic Acid Anhydrides

Most anhydrides are named by dropping the word acid from the name of the carboxylic acid and then adding the word anhydride.

Carboxylic acids react with acyl chlorides in the presence of pyridine to give carboxylic acid anhydrides. Sodium salts of carboxylic acids also react with acyl chlorides to give anhydrides.

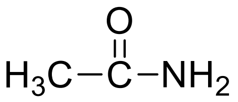


$$R-\overset{O}{\overset{\|}{C}}-Cl + Na^+O^--\overset{O}{\overset{\|}{C}}-R^1 \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R$$

4.13 Amides

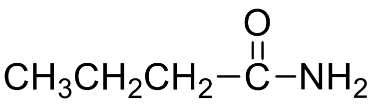
Amides that have no substituent on nitrogen are named by dropping -ic acid from the common name of the acid (or -oic acid from the substitutive name) and then adding -amide.

Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by N- or N,N-.



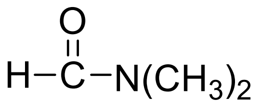
$H_3C-\overset{O}{\overset{\|}{C}}-NH_2$

Acetamide



$CH_3CH_2CH_2-\overset{O}{\overset{\|}{C}}-NH_2$

Butyramide



$H-\overset{O}{\overset{\|}{C}}-N(CH_3)_2$

N,*N*-dimethylformamide

Primary amines, secondary amines, and ammonia all react rapidly with acid chlorides to form amides.

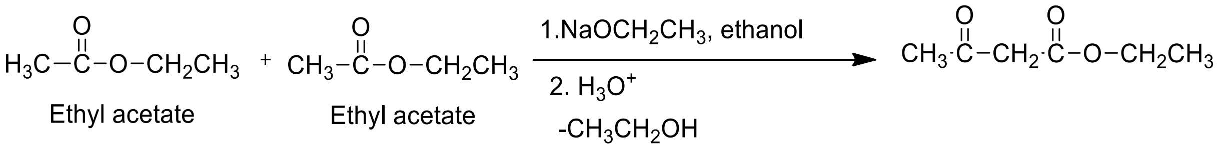
$$R-\overset{O}{\overset{\|}{C}}-Cl + NH_3 \xrightarrow{\text{Heat}} R-\overset{O}{\overset{\|}{C}}-NH_2 + HCl$$

Acid chloride

Amide

4.14 The Claisen condensation

The Claisen condensation is a carbon-carbon bond-forming reaction that is useful for synthesizing β-keto esters. In a Claisen condensation, the enolate of one ester molecule adds to the carbonyl group of another, resulting in an acyl substitution reaction that forms a β -keto ester and an alcohol molecule.



$$H_3C-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3 + CH_3-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3 \xrightarrow[\text{2. } H_3O^+ \quad -CH_3CH_2OH]{\text{1.}NaOCH_2CH_3\text{, ethanol}} CH_3\text{-}\overset{O}{\overset{\|}{C}}-CH_2\text{-}\overset{O}{\overset{\|}{C}}-O-CH_2CH_3$$

Ethyl acetate

Ethyl acetate